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Marks and Mechanisms: Unraveling Potential Health Impacts of PFAS via DNA Methylation

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Human exposure to per- and polyfluoroalkyl substances (PFAS) is ubiquitous.[1] Prenatal and early-life exposures to PFAS have been consistently associated with adverse health effects in children, especially metabolic and immune system disorders, yet we still know little about underlying mechanisms that might explain these associations.[2] The authors of a study recently published in *Environmental Health Perspectives*[3] assessed long-term changes in genome-wide DNA methylation to increase our understanding of these mechanisms.

Humans are exposed to mixtures of hundreds if not thousands of PFAS.[4,5] These chemicals, which are present in food, food packaging, and many everyday consumer products, have been detected in more than 98% of U.S. population serum samples.[6] In addition, an estimated 200 million Americans consume water with PFAS concentrations exceeding 1 ng/L, one of several health-based limits under regulatory consideration[7] (currently there is no national drinking water standard for PFAS).

For the present study, the investigators drew data from two prospective pregnancy and birth cohorts. The first included 266 children born between 2003 and 2006 who were enrolled in the Health Outcomes and Measures of the Environment (HOME) Study. Participants lived around Cincinnati, Ohio, in an area that has previously experienced PFAS contamination from industrial sources.[8] Data from 371 children in the Project Viva cohort,[9] born between 1999 and 2002 near Boston, Massachusetts, were used for the replication analysis.

Using the Illumina HumanMethylationEPIC BeadChip, Yun Liu and colleagues measured genome-wide DNA methylation in peripheral leukocytes collected from the cord blood of HOME Study newborns and in blood samples from the same children at 12 years of age. DNA methylation is an epigenetic feature that regulates gene expression without any alteration in DNA sequence.[10] It involves the transfer of methyl groups to short DNA stretches with repeated cytosine and guanine nucleotides (CpG sites), most of which are located in regions associated with gene expression.[10]

The researchers also measured four PFAS in maternal serum samples collected in the HOME Study[11]: two legacy chemicals that have been phased out (perfluorooctanoate and perfluorooctane sulfonate) and two newer chemicals (perfluorononanoate and perfluorohexane sulfonate).[12,13]

The new study, like earlier reports,[14–18] found that gestational PFAS exposure was associated with differences in DNA methylation patterns, despite variations in study design, demographics, measurement technology, and PFAS exposure levels. "For the first time, our longitudinal study also demonstrates that these epigenetic changes may persist for more than a decade," says Liu, the study's first author and a postdoctoral research associate at Brown University.

A new study, like earlier reports, found that gestational PFAS exposure was associated with specific DNA methylation patterns in newborns. However, the new longitudinal study further demonstrated that methylation patterns observed at birth largely persisted for more than a decade. Images, left to right: © iStockphoto/Olga Moreira; © Image Source Trading Ltd/Shutterstock.com.

The researchers found that gestational PFAS exposure was significantly associated with methylation at 435 CpG sites in newborns, with distinct sites for each of the four PFAS. Most of these associations remained at approximately 12 years of age. Six of these sites—two for perfluorooctanoate and four for perfluorononanoate—were replicated in the Project Viva cohort. Although the specific CpG sites differed from those reported previously,[14–18] most methylation differences observed in the earlier studies also occurred near genes related to PFAS-associated health outcomes, such as cancers and immune system, cardiovascular, and kidney disorders.

For Erin Bell, a professor of epidemiology at the University at Albany who was not involved in the study, this consistency across studies is compelling. "It suggests that gene expression regulation via DNA methylation is a pathway that deserves further study," she says. "The new finding that some of these changes may be stable over time will help us narrow down hypotheses about shared biological mechanisms that may contribute to multiple PFAS-related health outcomes."

To that end, the researchers are planning follow-up analyses to see "whether DNA methylation near specific genes may mediate the association between PFAS levels and markers of cardiometabolic health in the children of HOME Study participants," says Liu. Such mediation analyses[19] have, for example, identified DNA methylation as a potential link between fat and carbohydrate intake and metabolic traits.[20]

Lida Chatzi, a professor of population and public health sciences at the University of Southern California who was not involved in the study, applauds its longitudinal design. "Repeated measurements of epigenetic and omics-based biomarkers in large populations will be critical for investigating disease mechanisms," says Chatzi. "Ideally, this would also include moving from blood to tissue-specific studies of PFAS-associated health effects."

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